Endogenous Peptides and Protein Substances or Their Analogs

Endogenous peptides or proteins and their analogs, produced by chemical synthesis, by extraction/purification from an animal/human source or by biotechnological methods such as recombinant DNA technology may require special considerations.

Carcinogenicity studies are not generally needed for endogenous substances given essentially as replacement therapy (i.e., physiological levels), particularly where there is previous clinical experience with similar products (for example, animal insulins, pituitary-derived growth hormone, and calcitonin).

The need for carcinogenicity studies in rodent species should be considered if indicated by the treatment duration, clinical indication, or patient population (providing neutralizing antibodies are not elicited to such an extent in repeated dose studies as to invalidate the results). Carcinogenicity studies may be needed in the following circumstances: (1) For products where there are significant differences in biological effects to the natural counterpart(s); (2) for products where modifications lead to significant changes in structure compared to the natural counterpart; and (3) for products resulting in humans in a significant increase over the existing local or systemic concentration (i.e., pharmacological levels).

Need for Additional Testing

The relevance of the results obtained from animal carcinogenicity studies for assessment of human safety are often cause for debate. Further research may be needed, investigating the mode of action, which may result in confirming the presence or the lack of carcinogenic potential for humans. When it is considered important to evaluate the relevance of tumor findings in animals for human safety, mechanistic studies are essential.

Supplementary Notes

Note 1: Assessment of the genotoxic potential of a compound must take into account the totality of the findings and acknowledge the intrinsic value and limitations of both in vitro and in vivo tests. The test battery approach of in vitro and in vivo tests is designed to reduce the risk of false negative results for compounds with genotoxic potential. A positive result in any assay for genotoxicity does not necessarily mean that the test compound poses a genotoxic hazard to humans (reference ICH Safety Topic S2A).

Dated: August 14, 1995.

William K. Hubbard,

Acting Deputy Commissioner for Policy.

[FR Doc. 95–20610 Filed 8–18–95; 8:45 am]

BILLING CODE 4160–01–F

[Docket No. 93D–0140]

International Conference on Harmonisation; Draft Guideline on Detection of Toxicity to Reproduction: Addendum on Toxicity to Male Fertility; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing portions of a revised draft guideline entitled ''Detection of Toxicity to Reproduction: Addendum on Toxicity to Male Fertility.'' This draft guideline was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The draft guideline is intended to reflect sound scientific principles for reproductive toxicity testing concerning male fertility, and is an addendum to an earlier ICH guideline on the detection of toxicity to reproduction for medicinal products.

DATES: Written comments by October 5, 1995.

ADDRESSES: Submit written comments on the draft guideline to the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857. Copies of the draft guideline are available from the CDER Executive Secretariat Staff (HFD–8), Center for Drug Evaluation and Research, Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855.

FOR FURTHER INFORMATION CONTACT:

Regarding the guideline: Joy A. Cavagnaro, Center for Biologics Evaluation and Research (HFM–2), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852, 301–827–0379.

Regarding the ICH: Janet J. Showalter, Office of Health Affairs (HFY–20), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–0864.

SUPPLEMENTARY INFORMATION: In recent years, many important initiatives have been undertaken by regulatory authorities and industry associations to promote international harmonization of regulatory requirements. FDA has participated in many meetings designed to enhance harmonization and is committed to seeking scientifically based harmonized technical procedures for pharmaceutical development. One of the goals of harmonization is to identify and then reduce differences in technical requirements for drug development among regulatory agencies.

ICH was organized to provide an opportunity for tripartite harmonization initiatives to be developed with input from both regulatory and industry representatives. FDA also seeks input from consumer representatives and others. ICH is concerned with harmonization of technical requirements for the registration of pharmaceutical products among three regions: The European Union, Japan, and the United States. The six ICH sponsors are the European Commission, the European Federation of Pharmaceutical Industries Associations, the Japanese Ministry of Health and Welfare, the Japanese Pharmaceutical Manufacturers Association, the Centers for Drug Evaluation and Research and Biologics Evaluation and Research, FDA, and the Pharmaceutical Research and Manufacturers of America. The ICH Secretariat, which coordinates the preparation of documentation, is provided by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

The ICH Steering Committee includes representatives from each of the ICH sponsors and the IFPMA, as well as observers from the World Health Organization, the Canadian Health Protection Branch, and the European Free Trade Area.

At a meeting held on March 29, 1995, the ICH Steering Committee agreed that a draft guideline entitled ''Detection of Toxicity to Reproduction: Addendum on Toxicity to Male Fertility'' should be made available for public comment. The draft guideline is the product of the Safety Expert Working Group of the ICH. Comments about this draft will be considered by FDA and the Expert Working Group. Ultimately, FDA intends to adopt the ICH Steering Committee's final guideline.

This draft guideline is an addendum to an ICH final guideline published in the **Federal Register** of September 22, 1994 (59 FR 48746) entitled ''Guideline on Detection of Toxicity to Reproduction for Medicinal Products.'' This draft guideline is intended to reflect sound scientific principles for reproductive toxicity testing concerning male fertility.

In the past, guidelines have generally been issued under § 10.90(b) (21 CFR 10.90(b)), which provides for the use of guidelines to state procedures or standards of general applicability that are not legal requirements but are acceptable to FDA. The agency is now in the process of revising § 10.90(b). Therefore, this guideline is not being issued under the authority of § 10.90(b),

and it does not create or confer any rights, privileges, or benefits for or on any person, nor does it operate to bind FDA in any way.

Interested persons may, on or before October 5, 1995, submit to the Dockets Management Branch (address above) written comments on the draft guideline. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The draft guideline and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

The text of the draft guideline follows:

Detection of Toxicity to Reproduction: Addendum on Toxicity to Male Fertility

1. Introduction

1.1 Objective

Addendum to ICH—S5A Tripartite Guideline

1.2 Male fertility investigation, as included in the currently harmonized guideline, was accepted to recommend scientific and regulatory improvement and optimization of test designs.

1.3 Better description is needed of the testing concept and recommendations with regard to male fertility assessment, especially those addressing:

- Flexibility
- Premating treatment duration
- Observation

1.4 The general principles and background are contained in two papers accepted for publication to the *Journal of American College of Toxicology*.

These papers contain necessary experimental data (prospective and retrospective) for reaching consensus, and have been discussed among the expert working group. The ''raw data'' from the Japanese study will also be published.

1.5 The projected timeframe proposed:

—Step 2 in Washington, March 1995
—Step 3 in Brussels, July 1995
—Step 4 in Yokohama, November 1995

2. The guideline draft texts are attached.

3. For glossary see the harmonized S5—A guideline

Introduction

(Last paragraph revised)

To employ this concept successfully, flexibility is needed (Note 1). No guideline can provide sufficient information to cover all possible cases. All persons involved should be willing to discuss and consider variations in test strategy according to the state-of-the-art and ethical standards in human and animal experimentation. (*Delete next sentence*)

Note 12 (4.1.l) Premating Treatment

(Revised)

The design of the fertility study, especially the reduction in the premating period for males, is based on evidence accumulated and reappraisal of the basic research on the process of spermatogenesis. Compounds inducing selective effects on male reproduction are rare; compounds affecting spermatogenesis almost invariably affect postmeiotic stages; mating with females is an insensitive means of detecting effects on spermatogenesis. Histopathology of the testis has been shown to be the most sensitive method for the detection of effects on spermatogenesis. Good pathological and histopathological examination (e.g., by employing Bouin's fixation, paraffin embedding, transverse section of 2 to 4 microns for testes, longitudinal section for epididymides, PAS, and haematoxylin staining) of the male reproductive organs provides a quick direct means of detection. Sperm analysis (sperm counts and optionally sperm motility, sperm morphology) can be used as a method to confirm findings by other methods and to characterize effects further. Sperm are derived from the more mature stages. Samples from ejaculates, from vas deferens, or from cauda epididymis should be used. Information on potential effects on spermatogenesis (and female reproductive organs) can be derived from repeated dose toxicity studies.

For detection of effects unrelated to spermatogenesis (sperm abnormalities, mating behavior), mating with females after a premating treatment of 2 and 4 weeks has been shown to be at least as efficient as mating after a longer duration of treatment. When the available evidence suggests that the scope of investigations in the fertility study should be increased, appropriate studies should be designed to characterize the effects further.

Administration Period

(Revised)

The design assumes that, especially for effects on spermatogenesis, use will be made of data (e.g., histopathology and weight of reproductive organs, hormone assays, and genotoxicity data) from repeated dose toxicity studies. Provided no effects have been found that preclude this, a premating treatment interval of 2 weeks for females and 4 weeks for males (2 weeks may be acceptable in some cases) can be used (Note 12). Selection of the length of the premating administration period should be stated and justified (see also chapter 1.1, pointing out the need for research). Treatment should continue throughout mating to termination for males and at least through implantation for females. This will permit evaluation of functional effects on male fertility that cannot be detected by histologic examination in repeated dose toxicity studies and effects on mating behavior in both sexes. If data from other studies show there are effects on weight or histologic appearance of reproductive organs in males or females, or if the quality of examinations is dubious, or if there are no data from other studies, then a more comprehensive study should be designed (Note 12).

4.1.1 Study of Fertility and Early Embryonic Development to Implantation

Observations

(Revised)

At terminal examination, the following observations should be made:

- Necropsy (macroscopic examination) of all adults;
- Preserve organs with macroscopic findings for possible histological evaluation; keep corresponding organs of sufficient controls for comparison;
- Preserve testes, epididymides, ovaries, and uteri from all animals for possible histological examination and evaluation on a case-by-case basis;
- Count corpora lutea, implantation sites (Note 16);
- Live and dead conceptuses; and
- Sperm analysis as an optional procedure for confirmation or better characterization of an effect observed (Note 12).

Dated: August 14, 1995.

William K. Hubbard,

Acting Deputy Commissioner for Policy.

[FR Doc. 95–20609 Filed 8–18–95; 8:45 am]

BILLING CODE 4160–01–F

[Docket No. 93D–0139]

International Conference on Harmonisation; Draft Guideline on Stability Testing of Biotechnological/ Biological Products; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a draft guideline entitled ''Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products.'' This draft guideline was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The draft guideline is intended to give guidance to applicants regarding the type of stability studies that should be provided in support of marketing applications for biotechnological/ biological products.

DATES: Written comments by October 5, 1995.

ADDRESSES: Submit written comments on the draft guideline to the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857. Copies of the draft guideline are available from the CDER Executive Secretariat Staff (HFD–8), Center for Drug Evaluation and Research, Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, as well as the CBER Congressional and Consumer Affairs Branch (HFM–12), Center for Biologics Evaluation and Research,